

action of May 4, 2001. Applicants respectfully disagree. Paragraph #1 of the Office Action states that the finality of the previous Office Action was withdrawn, and the amendment and declaration filed on August 26, 2002 was entered. With the finality of the office action withdrawn, the declaration was effectively filed before a final action. MPEP 716.01 states that affidavits, declarations and other evidence traversing rejections "are considered timely if submitted: (1) prior to a final rejection". The requirement that a declaration be directed solely to a new ground of rejection or requirement is for declarations filed after a final rejection when the new ground of rejection was made in the final rejection. In the instant case, the declaration was filed with the RCE and thus before final rejection. Applicants respectfully request the examiner consider the timely-filed declaration, and if the declaration is deemed insufficient to overcome the enablement rejection, to please specifically explain why the evidence is insufficient.

The examiner states, under paragraph #7 of the Office Action, that because none of the articles listed on page 6 of the declaration were submitted, no showing has been made that supports the conclusion offered by the declarant. The declaration discusses the great number of articles published in 1995 related to differential display and subtractive hybridization as an indication that these methods were well-known and publicly available to the skilled artisan prior to the instant invention. Additionally, the Liang and Pardee article from 1992 (#2 on the list) was provided in an IDS filed December 10, 1998, and was considered by the Examiner on December 2, 1999 (see enclosed copy of initialed 1449). This reference teaches differential display as a method of separating and cloning individual mRNAs. Applicants believe the reference previously submitted and considered by the Examiner is representative of the numerous published articles related to the well-known techniques for determining mRNA expression. However, in the interest of advancing prosecution, Applicants submit herewith the remaining references to show that at the time of the invention, various methods for determining levels of mRNA expression were publicly available.

In paragraph #8 of the Office Action, the examiner states that arguments related to subtractive hybridization and differential display are not persuasive because these limitations are not found in the claims. However, claim 7 specifically recites the identification of differential gene expression is determined by differential display or

subtractive hybridization. Differential display and subtractive hybridization are just two examples of the many suitable methods of determining levels of mRNA expression. MPEP 2164.01(b), citing *In re Fisher* and *Spectra-Physics, Inc. v. coherent, Inc.*, states that as long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied, and the failure to disclose other methods by which the claimed invention may be made does not render a claim invalid. Applicants submit that the specification, in disclosing that one method of analyzing RNA is the differential display cloning procedure of Liang and Pardee, does enable the entire scope of the claimed methods.

Rejections under 35 U.S.C. §112, first paragraph

Claims 2, 3, 6-9 and 12 remain rejected as not enabled by the specification. The Examiner asserts that the specification does not provide reaction conditions, and that the situation is analogous to that in *Genentech v. Novo Nordisk*. Applicants respectfully traverse the rejection.

The examiner included the following quote from *Genentech v. Novo Nordisk*:

"It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research."

Applicants submit that the instant specification does supply the novel aspects of the invention. The asserted aspects of the invention the examiner refers to, such as reaction conditions for differential display cloning or other RNA analysis methods, fall in the category of what is well known in the art rather than a novel aspect of the invention. Specifically, on page 5, line 6, the specification states that "known gene cloning procedures" are used to analyze gene expression.

The specification clearly teaches that any known cloning procedures can be used; thus this is not a novel aspect of the invention. MPEP 2164.05(a), citing various cases, states "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." Applicants submit that reaction conditions and procedures for determining

levels of mRNA expression, such as differential display or subtractive hybridization, were well-known to those of ordinary skill in the art at the time the invention was made. For example, the specification cites a reference by Liang et al., published in 1992, for teaching differential display (see page 5, lines 6-8). This reference was submitted in an Information Disclosure Statement filed December 10, 1998 (copy enclosed). Thus, at the time of the instant invention, filed in 1996, differential display was well-known to those skilled in the art and was available to the public. Subtractive hybridization was also well-known and available to the public at the time of the invention, as evidenced by its discussion in the 1990 edition of *GENES IV* (copy enclosed). Additionally, as discussed in the declaration of Øystein Fodstad, there are numerous journal articles published prior to the filing date of the instant application that teach methods of determining levels of mRNA expression in various tissues. Copies of the articles are enclosed.

The novel aspect of the invention is the surprising finding that the same target cells in different tissues showed different gene expression which allowed the inventors to find new genes that are switched on or off in the different tissues. The invention involves using known method of comparing the expression levels of mRNA to identify genes differentially expressed in the same target cells from two different tissues.

The examiner asserts that the specification is essentially silent as to what starting materials are to be used in practicing the full scope of the claimed methods. Applicants respectfully disagree. The specification teaches, in Example 1 on page 5, lines 36-38, that tumor cells from primary tumor and auxiliary lymph nodes from a breast cancer patient were isolated and used in the claimed method. Example 4 on page 7, lines 29-35, describes performing the claimed method using tumor cells isolated from colorectal or prostate tumors, lymph nodes, liver metastasis, blood and bone marrow. Thus, the specification clearly teaches starting materials for practicing the claimed methods.

Applicants submit that, at the time of the invention, one of ordinary skill in the art would have known how to determine levels of mRNA expression in tissues using one of the well-known methods available to the public. As this is not the novel subject matter of the invention, Applicants submit that the specification, combined with the knowledge readily available to the skilled artisan, does enable one to practice the invention. Withdrawal of the rejection is respectfully requested.

The rejection of claim 2 has been repeated without any comments regarding the amended language. As stated in the previous response, Applicants are unsure how the claim has been interpreted as reciting the simultaneous screening of 12 or more different samples. Claim 2, as previously amended, clearly recites a listing of different tissues from which the first and second tissues recited in claim 12 could be taken. Applicants submit that claim 2 is fully supported and enabled by the specification as filed. If this rejection is maintained, Applicants respectfully request a more detailed explanation of how claim 2 is interpreted so that a further response can be prepared.

Claim 9 remains rejected as not enabled by the disclosure as it relates to studying the pattern of expression for the "identified genes". The Examiner maintains that the disclosure does not set forth a repeatable procedure whereby any gene has actually been identified and studied. As stated in the previous response, Example 2 on pages 6 and 7 of the specification teaches the discovery of two genes using the claimed method, LV1 and LV12, that are differentially expressed in MA-11 human breast cancer cells. The Examiner has not responded to this argument, but has added statements regarding the unpredictability of chemistry and cellular physiology. As the specification does provide an example of genes identified by the claimed method, this rejection is not understood. Withdrawal of the rejection is respectfully requested.

#### Conclusion

In view of the amendments, declaration and comments presented herein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested.

Respectfully submitted,

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